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## **Pro- or Anti-inflammatory Properties of the Adipokine Dipeptidyl Peptidase-4?**

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**Comment on: Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC**

**Pancreatitis, pancreatic, and thyroid cancer with glucagon-like Peptide-1-based therapies. Gastroenterology. 2011 Jul;141(1):150-6.**

# **Pro- or Anti-inflammatory Properties of the Adipokine Dipeptidyl Peptidase-4?**

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Conflict of interest statement

Giatgen A. Spinas and Markus Niessen have no conflict of interest. Linhua Xu will work for Novo Nordisk.

Dear Sir,

In the July 2011 issue Michael Elashoff and colleagues <sup>1</sup> reported an increased incidence of pancreatitis in diabetic subjects undergoing glucagon-like peptide (GLP)-1-based therapies. In light of the recently emerged and proliferating discussion about the clinical use and the associated risks of incretin-based therapies we would like to comment on this article and contribute evidence supporting the role of adipose-derived dipeptidyl peptidase (DPP)-4 in the context of the metabolic syndrome.

DPP-4 is found in many different tissues as a membrane-associated peptidase but also exists as a soluble form in plasma of humans and rodents. It cleaves and thereby inhibits GLP-1, which is secreted postprandially by intestinal L-cells to improve clearance of glucose from circulation (incretin effect). Several DPP-4 inhibitors are currently used to treat type 2 diabetes <sup>2</sup>. Recently, Daniela Lamers and colleagues <sup>3</sup> reported in the May 20<sup>th</sup> issue of *Diabetes* that adipocytes release DPP-4 into circulation, an observation that defines DPP-4 as an adipokine. We observed significant changes in the abundance of adipokines in supernatants collected from 3T3-L1 adipocytes cultured for 18 hours in the presence of the DPP-4 inhibitor (DPP-4i) sitagliptin. Among four different adipokines analysed adiponectin was increased (1.2 fold  $\pm$  0.07,  $p < 0.05$ ,  $n=4$ ) while MCP-1 and leptin remained unchanged. The increased accumulation of adiponectin in the presence DPP-4i is in line with the finding of Lamers and colleagues who described a negative correlation between the secretion of DPP-4 and adiponectin. In our experimental setting, we also found higher level of IL-6 (1.6 fold  $\pm$  0.06,  $p < 0.05$ ,  $n=4$ ) in the presence of DPP-4i. That DPP-4i promotes accumulation of a pro-inflammatory cytokine, however, supports the finding by Michael Elashoff and colleagues. Given the association between low-grade systemic inflammation and the development of type 2 diabetes an important yet unanswered question is if DPP-4 secreted by adipocytes is pro- or anti-inflammatory? As a caveat, however, it should be noted that our results were obtained with 3T3-L1 adipocytes *in vitro* and might not reflect the more complex *in vivo* situation.

Conclusive analysis of the physiological role of DPP-4 production by adipocytes, especially with a focus on its established interaction with cytokines and chemokines, appears desirable to ensure safe therapeutic use of DPP-4 inhibitors in the treatment of hyperglycaemia and type 2 diabetes.

1. Elashoff M, Matveyenko AV, Gier B, et al. **Pancreatitis, pancreatic, and thyroid cancer with glucagon-like Peptide-1-based therapies.** Gastroenterology 2011;141:150-6.
2. Drucker DJ, Nauck MA. **The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes.** Lancet 2006;368:1696-705.
3. Lamers D, Famulla S, Wronkowitz N, et al. **Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome.** Diabetes 2011;60:1917-25.